



## Research article

## Structural and functional brain network of human retrosplenial cortex

Panlong Li<sup>a,b</sup>, Han Shan<sup>d</sup>, Shengxiang Liang<sup>a,b</sup>, Binbin Nie<sup>b,c</sup>, Shaofeng Duan<sup>b,c</sup>, Qi Huang<sup>b,c</sup>, Tianhao Zhang<sup>b,c</sup>, Xi Sun<sup>a,b</sup>, Ting Feng<sup>a,b</sup>, Lin Ma<sup>d</sup>, Baoci Shan<sup>b,c,e,\*</sup>, Demin Li<sup>a,\*\*</sup>, Hua Liu<sup>b,c,\*</sup>

<sup>a</sup> Department of Physics, Zhengzhou University, Zhengzhou, Henan, 450001, China

<sup>b</sup> Beijing Engineering Research Center of Radiographic Techniques and Equipment, Institute of High Energy Physics, Chinese Academy of Sciences, Beijing, 100049, China

<sup>c</sup> School of Nuclear Science and Technology, University of Chinese Academy of Sciences, Beijing, 100049, China

<sup>d</sup> Department of Radiology, Chinese People's Liberation Army General Hospital, Beijing, 100853, China

<sup>e</sup> CAS Center for Excellence in Brain Science and Intelligence Technology, China



## ARTICLE INFO

## Keywords:

Retrosplenial cortex  
Cognitive function  
DTI tractography  
Functional MRI

## ABSTRACT

Retrosplenial cortex (RSC) plays a key role in various cognitive functions. The fiber connectivity of RSC had been reported in rodent and primate studies by tracer injection methods. To explore structural and functional connectivity of two sub-regions of RSC, Brodmann area (BA)29 and BA30, we constructed fiber connectivity networks of two sub-regions by diffusion tensor imaging (DTI) tractography based on diffusion magnetic resonance imaging (MRI) and functional connectivity networks by resting-state functional MRI. The BA29 network showed fiber connections with auditory cortex and functional connections with BA21. Both fiber and functional connections show that BA30 network includes visual cortex. Furthermore, BA30 had fiber connections with hippocampus, thalamus, and prefrontal cortex. We suggest that (1) structural connectivity reflects functional connectivity in some degree. (2) BA29 mainly received and processed sound information from auditory cortex, while BA30 mainly received and processed scene information from visual cortex.

## 1. Introduction

Animal and human studies have indicated that retrosplenial cortex (RSC) plays a key role in various cognitive functions, including spatial memory, navigation, as well as imagination and planning for the future [2,7,42]. These studies have almost always treated RSC as a single structure. In fact, RSC contains two major sub-regions—the granular (Brodmann area [BA]29) and dysgranular (BA30) areas [42].

It has been reported that BA30 has extensive interconnections with visual cortex including BA17 and BA18 in rat [39]. BA29 lesions produced small effect or no effect on a working memory task in the water maze [38], whereas the BA30 lesions disrupted allocentric performance of the water maze task [41]. These anatomical and functional data suggests that the two sub-regions play different roles in cognitive functions. Additionally, reciprocal connections with thalamic nuclei, anterior cingulate cortex, hippocampal formation are found both in rat and monkey studies [4,14,18–26,39,40]. This highly invasive techniques (i.e., antemortem injections to create cortical lesions) is not used with humans for ethical reasons.

Diffusion tensor imaging (DTI) tractography as the first non-

invasive, in-vivo technique for fiber tracing [6,24] has been applied in many studies [3,21]. A few studies have used DTI to partially explore the fiber connectivity of RSC [13,46]. A recent study reported that RSC has strong fiber connections with thalamus, frontal cortex, hippocampus, and parahippocampal cortex [45]. These human DTI tractography suggests that RSC has a complicated connectivity network which might be the structural basis of its multiple functions. However, most of previous studies treated RSC as a single structure. In fact, the two sub-regions had different structural connectivity and functional role [39,41]. Of note, it is still unclear how different sub-regions fiber connected to their associated networks to support cognitive functions of RSC in humans.

In this study, we hypothesized that BA29 and BA30 have distinct structural and functional networks. We constructed their structural brain networks based on DTI tractography and functional connectivity (FC) networks based on fMRI to explore the neural bases of BA29 and BA30 in cognitive functions of RSC.

\* Corresponding authors at: Beijing Engineering Research Center of Radiographic Techniques and Equipment, Institute of High Energy Physics, Chinese Academy of Sciences, Beijing, 100049, China.

\*\* Corresponding author at: Department of Physics, Zhengzhou University, Zhengzhou, 450001, China.  
E-mail addresses: [shanbc@ihep.ac.cn](mailto:shanbc@ihep.ac.cn) (B. Shan), [lidm@zzu.edu.cn](mailto:lidm@zzu.edu.cn) (D. Li), [liuhua@ihep.ac.cn](mailto:liuhua@ihep.ac.cn) (H. Liu).

<https://doi.org/10.1016/j.neulet.2018.03.016>

Received 25 December 2017; Received in revised form 7 March 2018; Accepted 8 March 2018

Available online 09 March 2018

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## 2. Materials and methods

The protocol for this study was approved by the ethics committee of Chinese People's Liberation Army General Hospital (CPLAGH).

### 2.1. Subjects

Twenty-three right-handed healthy young subjects (female: 9, age range: 18–29) were recruited from the local community. All subjects were physically healthy and had no history of neurological and psychiatric disease, or addiction of drugs, cigarette and alcohol. They were fully informed of the study procedures, and signed informed consent to participate in the study.

### 2.2. MRI data acquisition

All MRI data were acquired on a 3T GE scanner (DISCOVERY MR750) at CPLAGH. During scanning, their eyes were kept closed, and ears were fitted with soft earplugs. The DTI protocol was performed using a diffusion-weighted single-shot, spin-echo echo-planar imaging sequence with the following parameters: 18 nonlinear directions, diffusion weighting of  $b = 1000 \text{ s/mm}^2$ , an acquisition without diffusion weighting of  $b = 0$ , slice thickness of 3 mm, no slice gap, TR/TE of 6000 ms/63.5 ms with 2 averages, FOV of 240 mm, matrix of  $128 \times 128$ , axial slices of 46, voxel size of  $0.94 \times 0.94 \times 3 \text{ mm}^3$ . The total scanning time for DTI was 3 min and 48 s for each subject. One hundred and eighty resting-state volumes were collected using a multi-slice gradient-echo EPI sequence with the following parameters: slice thickness of 4 mm, no slice gap, TR/TE of 2000 ms/30 ms, FOV of 240 mm, matrix of  $64 \times 64$ , and voxel size of  $3.75 \times 3.75 \times 4 \text{ mm}^3$ . The total fMRI scanning time was 6 min for each subject. After DTI and functional MRI scanning, high resolution T1-weighted images for anatomical information were acquired with 3D FSPGR sequence (TR/TE of 6.7/2.8 ms; flip angle of  $15^\circ$ ; FOV of 224 mm, matrix of  $512 \times 512$ , 452 slices, and voxel size of  $0.44 \times 0.44 \times 0.55 \text{ mm}^3$ ).

### 2.3. Data processing

#### 2.3.1. Reconstruction of fiber connection network of RSC

DTI data were preprocessed using FSL (<http://www.fmrib.ox.ac.uk/fsl/index.html>). After motion and eddy current distortion effects were removed by affine registration, brains were extracted using FSL Brain Extraction Tool (BET) [33].

Tensor reconstruction and fiber tracking were applied by Diffusion Toolkit 0.6.4 and Trackvis 0.6.1 (<http://www.trackvis.org>). After fractional anisotropy (FA) maps were calculated, whole-brain fiber tractography was applied using a Fiber Association Continuous Tracking algorithm (FACT) by Diffusion Toolkit. The maximum turning angle threshold was set as  $35^\circ$  [30,35], and the minimum FA threshold was set as 0.2 [11]. Then all these individual tracts were spatially normalized into the Montreal Neurological Institute (MNI) space by nonlinear transformation methods using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>) [13]. In detail, tracts normalization were performed by: (a) coregistering T1-weighted image to its corresponding FA image, (b) calculating deformation field by normalizing coregistered T1-weighted image into the MNI space, (c) applying the deformation field to tracts and bring them into MNI space.

The WFU PickAtlas toolbox (<http://www.fil.ion.ucl.ac.uk/spm>) was used to create binary masks of each brain region in the MNI space. The Brodmann atlas was selected in the WFU PickAtlas toolbox to produce sixty-nine binary regions of interest (ROIs), involving the whole gray matter. The length of tracks less than 2 cm were discarded [11]. The spatially normalized tracts that pass through BA29 and each other ROIs were recorded [13] by Trackvis. The same procedure was applied to BA30 to get its structural connectivity network. Group-level connection maps in the common space were generated by counting, in each voxel,

the number of subjects who have a tract passing through that voxel [13].

#### 2.3.2. Reconstruction of resting-state FC network of RSC

All fMRI data were processed using DPARSF (Data Processing Assistant for Resting-State fMRI; <http://www.restfmri.net>) [5]. The data preprocessing was referred to the previous research [16], including: (i) slice timing; (ii) head motion correction; (iii) normalizing to MNI space (voxel size:  $3 \times 3 \times 3 \text{ mm}^3$ ); (iv) smoothing by 6 mm full width at half-maximum (FWHM); (v) linear detrending; (vi) band pass temporal filtering (0.01–0.1 Hz); (vii) regressing out nuisance covariates (Friston 24 head motion parameters, white matter signal, cerebrospinal fluid signal).

Binary mask of BA29 and BA30 was chosen to set as two seed regions. Time courses from all voxels within each sub-region were averaged and used as reference time courses. Pearson correlation coefficient was calculated between the time courses of each reference and voxel, and then under-went Fisher's z-score transformation. For each subjects, FC maps of two sub-regions were established and then analyzed in SPM12 using one sample *t*-test model for calculating group level FC maps. Brain regions were considered significant within a threshold of  $p < 0.01$  after Family-wise error corrected for multiple comparisons and cluster size  $> 100$ .

## 3. Results

### 3.1. Fiber connection networks

BA29 was primarily responsible for connections with auditory cortex (BA21, BA22 and BA41) (Fig. 1), while BA30 was connected mainly with visual cortex/visual association cortex (BA17, BA18, and BA19), prefrontal cortex (BA9 and BA10), somatosensory association cortex (BA7), ectosplenial area (BA26), posterior entorhinal cortex (BA28), parahippocampal gyrus (BA36), fusiform gyrus (BA37), and some subcortical structures (amygdala, thalamus nucleus, caudate nucleus and putamen) (Fig. 2). Common areas including BA18 and BA19, BA23, BA30, BA31, and BA13 were found in the two networks.

Fig. 3b shows the group-level map of the tracts using a subject count threshold. Voxels with tracts from fewer than 5 subjects were discarded for display. The group-level map shows that BA29 has fiber connections mainly with temporal cortex, insular cortex, and posterior cingulate cortex, while BA30 has fiber connections mainly with occipital areas, thalamic nucleus, hippocampus and prefrontal cortex. The number of streamlines in the two structural connectivity networks was shown in Table 1.

### 3.2. Resting-state FC network

BA29 had positive FC with temporal cortex (BA20 and BA21), angular gyrus (BA39), prefrontal cortex (BA8, BA9, BA10, and BA11), somatosensory association cortex (BA7), posterior cingulate area (BA31, BA30, BA23) visual association cortex (BA18 and BA19), and parahippocampal gyrus (BA36) (Fig. 3c). BA 30 had positive FC with temporal cortex (BA20 and BA21), visual cortex/visual association cortex (BA17, BA18 and BA19), somatosensory cortex/somatosensory association cortex (BA3 and BA7), angular gyrus (BA39), anterior cingulate cortex (BA24), posterior cingulate cortex (BA29 and BA31), parahippocampal gyrus (BA36), fusiform (BA37), primary motor cortex (BA4 and BA6), and prefrontal cortex (BA8, BA9, BA10, and BA11) (Fig. 3c).

After comparing their structural and functional networks of each sub-regions, connectivity similarity was found in these two modalities networks (Fig. 3). This similarity was especially evident in the network of BA30. Most of the brain areas in structural network of BA30 also emerged in functional network.

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